

WHAT IS CLAIMED IS:

1. A method for selecting at least one antigen-specific B cell from a mixture of cells, said method comprising:

- 5 (A) providing a mixture of cells comprising B cells;
- (B) providing a first composition comprising:
- (a) a first core particle with at least one first attachment site; and
- (b) at least one antigen or antigenic determinant with at least one
- 10 second attachment site, wherein said second attachment site being selected from the group consisting of:
- i. an attachment site not naturally occurring with said antigen or antigenic determinant; and
- ii. an attachment site naturally occurring with said antigen or antigenic determinant;
- 15 wherein said second attachment site is capable of association to said first attachment site; and
- wherein said antigen or antigenic determinant and said first core particle interact through said association to form an ordered and repetitive antigen array;
- 20 (C) contacting said mixture of cells with said first composition;
- (D) labeling said first composition with a first labeling compound;
- (E) labeling said B cells in said mixture of cells with a second labeling compound; and
- (F) selecting at least one B cell which is positive for said first and said
- 25 second labeling compound.

2. The method of claim 1, wherein said first core particle is selected from the group consisting of:

- 30 (a) a virus;
- (b) a virus-like particle;
- (c) a bacteriophage;
- (d) a bacterial pilus;
- (e) a viral capsid particle;

- (f) a virus-like particle of a RNA-phage; and
- (g) a recombinant form of (a), (b), (c), (d), (e), or (f).

3. The method of claim 1, wherein said first core particle is a virus-like particle.

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4. The method of claim 3, wherein said at least one antigen or antigenic determinant is bound to said virus-like particle.

5. The method of claim 3, wherein said virus-like particle comprises recombinant proteins, or fragments thereof, selected from the group consisting of:

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- (a) recombinant proteins of Hepatitis B virus;
- (b) recombinant proteins of measles virus;
- (c) recombinant proteins of Sindbis virus;
- (d) recombinant proteins of Rotavirus;
- (e) recombinant proteins of Foot-and-Mouth-Disease virus;
- (f) recombinant proteins of Retrovirus;
- (g) recombinant proteins of Norwalk virus;
- (h) recombinant proteins of Alphavirus;
- (i) recombinant proteins of human Papilloma virus;
- (j) recombinant proteins of Polyoma virus;
- (k) recombinant proteins of bacteriophages;
- (l) recombinant proteins of RNA-phages;
- (m) recombinant proteins of Ty;
- (n) recombinant proteins of Q β -phage;
- (o) recombinant proteins of GA-phage;
- (p) recombinant proteins of fr-phage;
- (q) fragments of any of the recombinant proteins from (a) to (p);
and
- (r) variants of any of the recombinant proteins from (a) to (q).

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6. The method of claim 3, wherein said virus-like particle is Hepatitis B virus core antigen.

7. The method of claim 3, wherein said virus-like particle comprises recombinant proteins, or fragments thereof, of a RNA-phage.

8. The method of claim 7, wherein said RNA-phage is selected from the group consisting of:

- (a) bacteriophage Q β ;
- (b) bacteriophage R17;
- (c) bacteriophage fr;
- (d) bacteriophage GA;
- (e) bacteriophage SP;
- (f) bacteriophage MS2;
- (g) bacteriophage M11;
- (h) bacteriophage MX1;
- (i) bacteriophage NL95;
- (j) bacteriophage f2;
- (k) bacteriophage PP7; and
- (l) bacteriophage AP205.

9. The method of claim 3, wherein said virus-like particle comprises recombinant proteins, or fragments thereof, of RNA-phage Q β .

10. The method of claim 1, wherein said second attachment site of said first composition is capable of association to said first attachment site through at least one covalent bond.

11. The method of claim 10, wherein said covalent bond is a non-peptide bond.

12. The method of claim 1, wherein said antigen or antigenic determinant is selected from the group consisting of:

- (a) polypeptides;
- (b) carbohydrates;
- (c) steroid hormones;
- (d) organic molecules;

- (e) viruses;
- (f) bacteria;
- (g) parasites;
- (h) prions;
- (i) tumors;
- (j) self-molecules;
- (k) non-peptide hapten molecules; and
- (l) allergens.

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13. The method of claim 1, wherein said antigen or antigenic determinant is attached to said first core particle at high density.

14. The method of claim 1, wherein said antigen or antigenic determinant is attached to said first core particle at low density.

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15. The method of claim 1, further comprising the step of isolating said at least one antigen-specific B cell which is positive for said first and said second labeling compound.

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16. The method of claim 1, further comprising verifying specific antibody production of said selected at least one B cell.

17. The method of claim 16, wherein said verifying specific antibody production of said selected at least one antigen-specific B cell is effected by ELISA.

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18. The method of claim 1, wherein said selecting at least one B cell which is positive for said first and said second labeling compound is effected by using a first device capable of detecting said first labeling compound and a second device capable of detecting said second labeling compound.

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19. The method of claim 1, wherein said first labeling compound is a first fluorochrome.

20. The method of claim 1, wherein said second labeling compound is a second fluorochrome.

21. The method of claim 18, wherein said first labeling compound is a first
5 fluorochrome and said second labeling compound is a second fluorochrome, said first fluorochrome yielding a color different from said second fluorochrome upon activation, and wherein said first device capable of detecting said first labeling compound and said second device capable of detecting said second labeling compound is a fluorescence activated cell sorting apparatus (FACS).

10 22. The method of claim 1, wherein said labeling of said first composition is effected prior to contacting said mixture of cells with said first composition.

15 23. The method of claim 1, wherein said labeling of said first composition is effected after contacting said mixture of cells with said first composition.

20 24. The method of claim 23, wherein said labeling is effected with at least one antibody probe, wherein said probe comprises an antibody which is specific for said first composition, said antibody being conjugated with said first labeling compound.

25 25. The method of claim 24, wherein said first labeling compound is a first fluorochrome.

30 26. The method of claim 25, wherein said second labeling compound is a second fluorochrome, said first fluorochrome yielding a color different from said second fluorochrome upon activation, and wherein said selecting at least one B cell which is positive for said first and said second labeling compound is effected by using a first device capable of detecting said first labeling compound and a second device capable of detecting said second labeling compound, and wherein said first device capable of detecting said first labeling compound and said second device capable of detecting said second labeling compound is a fluorescence activated cell sorting apparatus (FACS).

27. The method of claim 24, wherein said antibody is specific for said first core particle of said first composition.

5 28. The method of claim 23, wherein said labeling is effected with at least one first antibody probe, wherein said first probe comprises a first antibody which is specific for said first composition, and at least one second antibody probe, wherein said second probe comprises a second antibody which is specific for said first antibody, said second antibody being conjugated with said first labeling
10 compound.

29. The method of claim 28, wherein said first labeling compound is a first fluorochrome.

15 30. The method of claim 29, wherein said second labeling compound is a second fluorochrome, said first fluorochrome yielding a color different from said second fluorochrome upon activation, and wherein said selecting at least one B cell which is positive for said first and said second labeling compound is effected by using a first device capable of detecting said first labeling compound and a second device
20 capable of detecting said second labeling compound, and wherein said first device capable of detecting said first labeling compound and said second device capable of detecting said second labeling compound is a fluorescence activated cell sorting apparatus (FACS).

25 31. The method of claim 28, wherein said first antibody is specific for said first core particle of said first composition.

30 32. The method of claim 1, wherein said labeling of said B cells is effected with a first set of at least one first targeting molecule, wherein said first targeting molecule is specific for at least one B cell marker, and wherein said first targeting molecule is labeled with said second labeling compound.

33. The method of claim 32, wherein said second labeling compound is a second fluorochrome.

34. The method of claim 33, wherein said first labeling compound is a first fluorochrome, said first fluorochrome yielding a color different from said second fluorochrome upon activation, and wherein said selecting at least one B cell which is positive for said first and said second labeling compound is effected by using a first device capable of detecting said first labeling compound and a second device capable of detecting said second labeling compound, and wherein said first device capable of detecting said first labeling compound and said second device capable of detecting said second labeling compound is a fluorescence activated cell sorting apparatus (FACS).

35. The method of claim 32, wherein said first targeting molecule is F(ab')₂ specific for IgG.

36. The method of claim 32, wherein said B cell marker is selected from the group consisting of molecules expressed by B cells, such as:

- (a) the surface IgG,
- (b) kappa and lambda chains,
- (c) CD19,
- (d) Ia,
- (e) Fc receptors,
- (f) B220,
- (g) CD20,
- (h) CD21,
- (i) CD22,
- (j) CD23,
- (k) CD79, or
- (l) CD81.

37. The method of claim 1, further comprising labeling said mixture with a second set of at least one second additional targeting molecule, wherein said at least one

second targeting molecule is specific for at least one marker unique for cells other than isotype-switched B cells, and wherein said at least one second targeting molecule is labeled with a third labeling compound.

- 5 38. The method of claim 37, wherein said third labeling compound is a third fluorochrome.
- 10 39. The method of claim 37, wherein said first labeling compound is a first fluorochrome, said second labeling compound is a second fluorochrome, and said third labeling compound is a third fluorochrome, said first, second, and third fluorochromes yielding different colors upon activation.
- 15 40. The method of claim 37, wherein said at least one marker unique for cells other than switched B cells is selected from the group consisting of at least one of IgD, IgM, CD3, CD4, CD8, CD11b, CD43 or Gr-1.
41. The method of claim 1 further comprising an additional step of adding a dead cell marker to said mixture of cells.
- 20 42. The method of claim 1, wherein said mixture of cells is a mixture of splenocytes.
43. The method of claim 1, wherein said mixture of cells is a mixture of peripheral blood cells.
- 25 44. The method of claim 1, wherein said mixture of cells is a mixture of splenocytes from immunized animals, said animals being immunized with a second composition comprising:
- (a) a second core particle with at least one first attachment site;
and
 - 30 (b) at least one antigen or antigenic determinant with at least one second attachment site, wherein said second attachment site being selected from the group consisting of:

- i. an attachment site not naturally occurring with said antigen or antigenic determinant; and
- ii. an attachment site naturally occurring with said antigen or antigenic determinant,

wherein said second attachment site is capable of association to said first attachment site; and

wherein said antigen or antigenic determinant and said second core particle interact through said association to form an ordered and repetitive antigen array.

45. The method of claim 44, wherein said second core particle is different from said first core particle.

46. The method of claim 44, wherein said second core particle is selected from the group consisting of:

- (a) a virus;
- (b) a virus-like particle;
- (c) a bacteriophage;
- (d) a bacterial pilus;
- (e) a viral capsid particle;
- (f) a virus-like particle of a RNA-phage; and
- (g) a recombinant form of (a), (b), (c), (d), (e), or (f).

47. The method of claim 44, wherein said second core particle is a virus-like particle.

48. The method of claim 47, wherein said at least one antigen or antigenic determinant is bound to said virus-like particle.

49. The method of claim 47, wherein said virus-like particle comprises recombinant proteins, or fragments thereof, selected from the group consisting of:

- (a) recombinant proteins of Hepatitis B virus;
- (b) recombinant proteins of measles virus;
- (c) recombinant proteins of Sindbis virus;

- (d) recombinant proteins of Rotavirus;
- (e) recombinant proteins of Foot-and-Mouth-Disease virus;
- (f) recombinant proteins of Retrovirus;
- (g) recombinant proteins of Norwalk virus;
- (h) recombinant proteins of Alphavirus;
- (i) recombinant proteins of human Papilloma virus;
- (j) recombinant proteins of Polyoma virus;
- (k) recombinant proteins of bacteriophages;
- (l) recombinant proteins of RNA-phages;
- (m) recombinant proteins of Ty;
- (n) recombinant proteins of Q β -phage;
- (o) recombinant proteins of GA-phage;
- (p) recombinant proteins of fr-phage;
- (q) fragments of any of the recombinant proteins from (a) to (p);
- and
- (r) variants of any of the recombinant proteins from (a) to (q).

50. The method of claim 47, wherein said virus-like particle is Hepatitis B virus core antigen.

51. The method of claim 47, wherein said virus-like particle comprises recombinant proteins, or fragments thereof, of a RNA-phage.

52. The method of claim 51, wherein said RNA-phage is selected from the group consisting of:

- (a) bacteriophage Q β ;
- (b) bacteriophage R17;
- (c) bacteriophage fr;
- (d) bacteriophage GA;
- (e) bacteriophage SP;
- (f) bacteriophage MS2;
- (g) bacteriophage M11;
- (h) bacteriophage MX1;

- (i) bacteriophage NL95;
- (j) bacteriophage f2;
- (k) bacteriophage PP7; and
- (l) bacteriophage AP205.

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53. The method of claim 47, wherein said virus-like particle comprises recombinant proteins, or fragments thereof, of RNA-phage Q β .

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54. The method of claim 44, wherein said second attachment site of said second composition is capable of association to said first attachment site through at least one covalent bond.

55. The method of claim 44, wherein said covalent bond is a non-peptide bond.

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56. The method of claim 44, wherein said antigen or antigenic determinant is selected from the group consisting of:

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- (a) polypeptides;
- (b) carbohydrates;
- (c) steroid hormones;
- (d) organic molecules;
- (e) viruses;
- (f) bacteria;
- (g) parasites;
- (h) prions;
- (i) tumors;
- (j) self-molecules;
- (k) non-peptide hapten molecules; and
- (l) allergens.

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57. The method of claim 44, wherein said antigen or antigenic determinant of said second composition is the same as said antigen or antigenic determinant of said first composition.

58. An antigen-specific B cell selected by the method of claim 1.

59. A method for generating monoclonal antibodies comprising the steps of providing at least one antigen-specific B cell selected by the method of claim 1 and fusing said at least one antigen-specific B cell with a myeloma cell line.

60. A method for generating monoclonal antibodies comprising the steps providing at least one antigen-specific B cell selected by the method of claim 44 and fusing said at least one antigen-specific B cell with a myeloma cell line.

61. A method for generating monoclonal antibodies or antibody fragments comprising the steps of isolating at least one genetic element encoding the immunoglobulin or parts of the immunoglobulin expressed by said at least one antigen-specific B cell selected by the method of claim 1 and expressing said genetic element.

62. The method of claim 61, wherein said genetic element is expressed as a fusion molecule.